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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,584	05/23/2006	Johannes Maria Franciscus Gerardus Aerts	Q94706	3068

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EXAMINER	
BAEK, BONG-SOOK	
ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/595,584	AERTS, JOHANNES MARIA FRANCISCUS GERARD	
	Examiner	Art Unit	
	BONG-SOOK BAEK	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,13 and 15-17* is/are pending in the application.

4a) Of the above claim(s) *16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-13, 15 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/28/2006 and 1/21/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 12-13 and 15-17 are currently pending.

Election/Restrictions

Applicants' election of group III (method claims) and election of the following species: insulin resistance as a single disclosed species of different disease conditions, in the reply filed on 1/21/2009 are acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a))

Claim 16 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Claims 12-13, 15 and 17 are under examination in the instant office action.

Priority

The instant application is a 371 of PCT/NL04/00760 filed on 10/29/2004 and claims benefit of foreign applications filed on 10/29/2003 and 7/6/2004. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). Certified copies of foreign applications have been submitted on 4/28/2006.

The earliest effective U.S. filing date afforded the instantly claimed invention has been determined to be 10/29/2004.

Information Disclosure Statement

Signed and initialed copies of the information disclosure statement filed on 4/28/2006 and 1/21/2009 are enclosed in this action. Foreign patent documents cited in the IDS filed on 1/21/2009 are not considered since Applicants did not provide copies of those documents.

Claim objections

Claims 12 and 13 are objected because of the following informalities: typographical errors. The phrase "consisting of" in line 7 should not be deleted and ".beta." should be corrected to --β--. Also, the term "the Method" should be corrected to --"The method" --.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitations of "derivative of deoxynojirimycin....., wherein said derivative comprising" in claim 12 render the claim herein indefinite. The term of "derivative" is not clearly defined in the specification and therefore does not set forth the metes and bounds of the

term "derivative". In addition, since open language "comprising, which allow additional elements, is used, the derivative of deoxynojirimycin can have any additional moieties or constituents, which are not recited. The 10th edition of the Merriam-Webster's Collegiate Dictionary (Merriam-Webster Incorporated: Springfield, Massachusetts, 1993, pp 311) defines "derivative" as "a chemical substance related structurally to another substance and theoretically derivable from it." Hence, one of ordinary skill in the art could not ascertain and interpret the metes and bounds of the patent protection desired as to "derivative of deoxynojirimycin" herein. Thus, it is unclear and indefinite as to how the "derivative of deoxynojirimycin" herein is encompassed thereby. Claim 13 is included since it incorporates the limitation of claim 12.

Claim 13 is further rejected because the expression "derived from" in line 2 fails to impart objective or otherwise sufficient metes and bounds such that one skilled in the art would be aware that he/she is infringing upon the subject matter which Applicant seeks to patent. Subjective subject matter is not definite subject matter.

In addition, claim 13 recites "the method of treatment of claim 12, wherein said derivative further comprises an polar side chain derived from a polycyclic alcohol containing three or more rings each sharing two or more carbon atoms with another ring and is capable of inserting in lipid bilayers, and a spacer comprising an alkoxy polyalkene or polyalkene chain of from 3 to 8 carbon atoms". It is unclear whether the apolar side chain and the spacer are further linked to the derivative in addition to the large hydrophobic moiety recited in claim 12 or the large hydrophobic moiety comprises an apolar side chain and the spacer. Also, it is unclear whether the derivative is capable of inserting in lipid bilayers or the apolar side chain is. In addition, the recitation of "a spacer comprising……." is unclear whether the spacer can have

additional moieties or substituents in addition to the alkoxy polyalkene or polyalkene chain since open language "comprising" allows additional elements.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-13 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating insulin resistance with N (5-adamantane- l-yl-methoxy-pentyl)deoxynojirimycina, does not reasonably provide enablement for treating hyperpigmentation and/or inflammatory skin conditions, overweight and obesity, fungal diseases, and microbacterial infections with the claimed deoxynojirimycin derivatives. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Attention is directed to *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. All factors have been considered together and specifically relevant factors are addressed below:

The nature of the invention and the breadth of the claims. The claims are drawn to a method for treating insulin resistance, hyperpigmentation and/or inflammatory skin conditions, overweight and obesity, fungal diseases, and microbacterial infections with a composition comprising administration of a deoxynojirimycin derivative.

The claims are very broad since the claims embrace the treatment of various diseases which have different etiology and pathophysiology.

The state of the prior art: Generally, the relative skill of those in the art of pharmaceuticals and pharmacology is high. Applicant has not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant composition for accomplishing the desired result of the claimed invention without undue experimentation. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970).

The predictability or unpredictability of the art: Insulin resistance, defined as a smaller than expected biological response to a given dose of insulin, is a ubiquitous correlate of obesity and most NIDDM patients are obese, and a very central and early component in the development of NIDDM is insulin resistance (see US 2003/0100504 cited in the 103 rejection). Insulin resistance or diabetes are common complications of obesity, however, the agents effective for treating insulin resistance or diabetes are not necessarily effective for treating obesity or overweight. Also, inflammatory skin condition, fungal disease or microbacterial infections are associated with fungal or bacterial infection, thus those conditions are treatable by antifungal

agent or antibiotics. The instant specification disclosed that the claimed compounds inhibit the synthesis of glucosylceramide and/or other glycosphingolipids and administration of N-(5-adamantane-1-yl-methoxy-pentyl)deoxynojirimycin by food resulted in the obese and diabetes mice (in dose-dependent) in reductions of blood glucose and water intake. However, there is no known prior art teaching that the alleged inhibitory effects on the synthesis of glucosylceramide and/or other glycosphingolipids or reduction of blood glucose and water intake would also be useful for treating fungal or bacterial infection. One skilled in the art would not expect that the agents effective for reducing blood glucose is also be predicatively used for treating inflammatory skin condition, fungal disease or microbacterial infections, which have different etiology and pathophysiology from those of diabetes. Therefore, treating insulin resistance, hyperpigmentation and/or inflammatory skin conditions, overweight and obesity, fungal diseases, and microbacterial infections, which have different etiology, by administering a deoxynojirimycin derivative is highly unpredictable to. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

The amount of direction or guidance presented and the presence or absence of working examples: Applicants disclosed *in vitro* and *in vivo* assays showing the effects of N-(5-adamantane-1-yl-methoxy-pentyl) deoxynojirimycin on inhibition of synthesis of glucosylceramide and/or other glycosphingolipids and reductions of blood glucose and water intake in the obese and diabetes mice by (p12-15). However, there is no disclosure regarding treating the other conditions such as hyperpigmentation and/or inflammatory skin conditions, overweight and obesity, fungal diseases, and microbacterial infections. There is no demonstrated

correlation that the disclosed tests and results apply to the other conditions. In addition, *in vitro* and *in vivo* assays do not always correlate to efficacy in humans and are not generally predictive of clinical efficacy. Furthermore, the specification provides no direction or guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to treat all of the various conditions recited in the instant claims, particularly in humans. The dosage regimen used for treating insulin resistance would be applied for treating hyperpigmentation and/or inflammatory skin conditions, fungal diseases, or microbacterial infections?

The Quantity of Experimentation Needed. Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed composition could be predictably used as a treatment of insulin resistance, hyperpigmentation and/or inflammatory skin conditions, overweight and obesity, fungal diseases, and microbacterial infections. Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

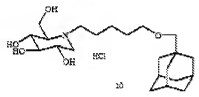
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 12-13, 15 and 17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over US patent 6,177,447 (cited by Applicant in the IDS filed on 1/21/2009) in view of Matsumoto *et al.* (Anal Chim Acta, 1479:135-141, March 2003) and in further view of US 2003/0100504 (pub date 5/29/2003).

US patent 6,177,447 teaches deoxynojirimycin derivatives containing a large hydrophobic moiety such as cholesterol or adamantane-methanol, linked through a spacer such as pentamethylene to the nitrogen atom of deoxynojirimycin, and salts thereof (abstract). The following N-(5-adamantane-1-yl-methoxy-pentyl)-deoxynojirimycin, which is the same compound as recited in the instant claims 15 and 17, is disclosed as an exemplary compound (column 10, lines 16-19 and scheme 2):



It further teaches the large hydrophobic moiety is derived from a polycyclic alcohol containing three or more rings each sharing two or more carbon atoms with another ring and has the ability to insert in lipid bilayers (column 5, line 65-column 6, lines 2) . In addition, it discloses a number of known glucosidase inhibitors such as D-gluconolacton, castanospermine, deoxynojirimycin and butyl-_deoxynojirimycin (column 8, lines 26-28).

The reference differs from the instant claims insofar as it does not specifically teach the use of the deoxynojirimycin derivative such as N-(5-adamantane-1-yl-methoxy-pentyl)-deoxynojirimycin for the treatment of insulin resistance.

Matsumoto *et al.* teaches 1- deoxynojirimycin as an inhibitor of α-glucosidase, which is a medicinal inhibitor for diabetes. (abstract). It further teaches that α-glucosidase is a membrane-bound enzyme at the epithelium of the small intestine that catalyzes the cleavage of glucose from disaccharide, and inhibitors of α-glucosidase are effective for delaying glucose absorption and have been used for the therapeutic treatment of non-insulin-dependent diabetes (NIDDM) (p135, column 1, para 1-column 2, para 2).

US 2003/0100504 teaches that insulin resistance, defined as a smaller than expected biological response to a given dose of insulin, is a ubiquitous correlate of obesity and most NIDDM patients are obese, and a very central and early component in the development of

NIDDM is insulin resistance ([0005)]), which suggests that the patient population suffering from NIDDM substantially overlaps with the patient population suffering from insulin resistance. In addition, US 2003/0100504 disclosed and α-glucosidase inhibitors such as miglitol and emiglitate (deoxynojirimycin derivatives) as an "insulin-resistance treating agent" or "hypoglycemic agent" (used interchangeably herein), which is used to treat an insulin-resistant disorder ([0084]).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the deoxynojirimycin derivative such as N-(5-adamantane-1-yl-methoxy-pentyl)-deoxynojirimycin taught by US patent 6,177,447 for treating insulin resistance with a reasonable expectation of success because of the following reasons: deoxynojirimycin derivatives are taught be a α-glucosidase inhibitor, which has been known to be effective for treating NIDDM and insulin resistance by prior art. US patent 6,177,447 teaches that the large hydrophobic moiety linked to deoxynojirimycin has the ability to insert in lipid bilayers. Thus, the skilled artisan would have been motivated to try the deoxynojirimycin derivative such as N-(5-adamantane-1-yl-methoxy-pentyl)-deoxynojirimycin taught by US patent 6,177,447 for treating patients suffering from insulin resistance which is correlated with NIDD and would have expected that it would function similarly to other deoxynojirimycin derivatives as miglitol and emiglitate taught by the prior art because he/she would have recognized the deoxynojirimycin as a functional group having inhibitory activity of α-glucosidase and the large hydrophobic moiety attached to the deoxynojirimycin as a carrier to target to the membrane-bound α-glucosidase.

Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 12-13, 15 and 17 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 18 of patent 7,528,153 (10/595589). Although the conflicting claims are not identical, they are not patentably distinct from each other because both the '455 application claims and the instant claims are drawn to a method of treating insulin resistance comprising administration of the same deoxynojirimycin derivative having a large hydrophobic moiety and a spacer such as N (5-adamantane- l-yl-methoxy-pentyl)deoxynojirimycin.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BONG-SOOK BAEK whose telephone number is 571-270-5863. The examiner can normally be reached 9:00-6:00 Monday-Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-071818. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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